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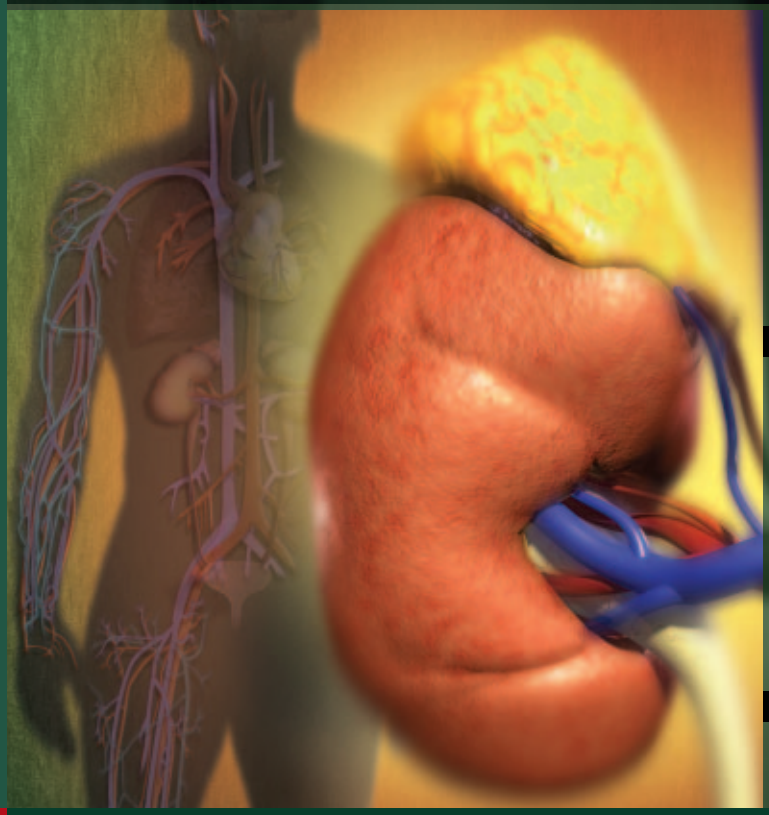
Implications of PRESERVING LONG-TERM RENAL FUNCTION After Renal Transplantation

PRESENTED BY:

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES OF THE NATIONAL INSTITUTES OF HEALTH U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Epidemiology of Renal Dysfunction and Cardiovascular Disease



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Educational Objectives

Upon completion of this program, the participant should be able to:

- Discuss cardiovascular risk factors among renal transplant recipients, including long-term renal dysfunction
- Describe the importance of preserving long-term renal function
- Discuss the mechanisms of renal allograft nephropathy and cardiovascular disease
- Describe immunosuppressive protocols, including calcineurin-sparing and steroid-sparing immunosuppressive protocols, and their effect on optimal long-term renal function

Target Audience

Transplant surgeons, transplant nephrologists, transplant nurses, transplant coordinators, and other healthcare professionals who are involved in the treatment and management of renal transplant recipients.

Term of Approval

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Epidemiology of Renal Dysfunction and Cardiovascular Disease

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Introduction

The cardiovascular risk associated with chronic kidney disease is significant and often underappreciated. According to estimates based on data from the Third National Health and Nutrition Examination Survey (NHANES III), a prospective study of a large representative sample of the general population in the United States, approximately 8 million adults (persons aged 20 years and older) have chronic kidney disease.[1] Both its incidence and prevalence are increasing. In this population, cardiovascular disease accounts for substantial morbidity and is the leading cause of death.[2]

As the understanding of shared metabolic, neuroendocrine, and physiological factors that modulate renal and cardiovascular function expands, the prevalence of cardiovascular disease in patients with chronic kidney disease appears almost inevitable. However, the precise mechanisms connecting renal function and cardiovascular risk and the optimal therapeutic approaches to reduce that risk in chronic kidney disease patients remain to be discerned.

Another question that arises is the direction of causality between cardiovascular disease and renal dysfunction. Numerous studies have suggested that treatment with antihypertensive agents can slow the progression of renal disease. In several of these studies, the observed reno-protective effects were greater than what was expected for blood pressure lowering alone, suggesting a more complex effect.[3-8] These findings, coupled with the reduced risk of cardiovascular mortality following transplantation, suggest that the relationship between renal insufficiency and cardiovascular disease may in fact occur in a bi-directional manner. However, the impact of early cardiovascular disease treatment on long-term outcomes for patients following renal transplantation has not been determined.

In an effort to address some of these unanswered questions, the Chronic Renal Insufficiency Cohort (CRIC) study, a longitudinal study of renal insufficiency and cardiovascular disease, is currently examining patterns of comorbidity and shared risk factors. The objective is to reduce the burden of advanced renal disease and cardiovascular disease by identifying and treating those individuals at highest risk of comorbidity.[9]

The link between renal dysfunction and cardiovascular disease in transplant recipients shares conceptual similarities to the relationship in the general population. These similarities can offer insight into the most important risk factors for the transplant population. This CLINICIAN® is based on presentations at a roundtable held in November 2003, presented by the National Institute of Allergy and Infectious Diseases and entitled, *Implications of Preserving Long-Term Renal Function After Renal Transplantation*. It is the first in a series of educational activities directed at raising awareness of the importance of cardiovascular disease in the transplant population. The present CLINICIAN is a synthesis of presentations by Drs Akinlolu O. Ojo, Bertram L. Kasiske, and Donald E. Hricik and examines the epidemiology of renal dysfunction and its relationship to cardiovascular disease in the general population as a basis for understanding the problems that may be specific to transplant patients.

Defining Renal Dysfunction in the General Population

Recently, a National Kidney Foundation Disease Outcomes Quality Initiative (K/DOQI) Work Group proposed a uniform classification system for chronic kidney disease based on the glomerular filtration rate (GFR). This overall measure of kidney function is defined by either kidney damage due to structural or functional abnormalities of the kidney that result in pathological abnormalities or markers of kidney damage including urine, blood, or imaging test abnormalities regardless of GFR; or GFR <60 mL/min/1.73 m^2 for ≥3 months with or without kidney damage.[2]

The Work Group also staged the level of severity of chronic kidney disease (Table 1). Individuals with stage 1 chronic kidney disease risk factors or kidney damage are candidates for early intervention to reduce chronic kidney disease and cardiovascular disease risk. Patients with stage 2 or 3 chronic kidney disease are considered to have mild or moderate renal dysfunction, respectively. Stages 4 and 5 are categorized as severe renal disease.[2]

Estimates of GFR based on surrogate measures of kidney function, such as serum creatinine (Cr) levels or creatinine clearance (Cr_{CL}), are used frequently because absolute measures of GFR are not practical for routine use. However, factors other than glomerular filtration of creatinine can influence serum Cr concentrations, and when this occurs, these values lose their validity as a measure of GFR. However, as a basis for comparison

Table 1

Stages of Chronic Kidney Disease[2]

Stage	GFR (mL/min/1.73 m^2)	Prevalence in United States* N (×1000)	Prevalence in United States* (%)
1	≥90	5900	3.3
2	60-89	5300	3.0
3	30-59	7600	4.3
4	15-29	400	0.2
5	<15 (or dialysis)	300	0.1

*Data from NHANES III (stages 1-4) and USRDS 1998 (stage 5).

among the studies described, a serum Cr concentration ≥1.4 mg/dL (124 µmol/L) is a good indicator of a GFR approximating 80 mL/min/1.73 m^2 among individuals aged 55 years and older.[10,11]

The majority of the approximately 8 to 10 million Americans who meet the National Kidney Foundation criteria for chronic kidney disease have mild-to-moderate renal dysfunction[2] (Table 1). In fact, the highest mortality and greatest economic burden of chronic kidney disease occur in such patients with mild-to-moderate chronic kidney disease, rather than in those on dialysis; furthermore, many of the patients with mild-to-moderate chronic kidney disease will die of cardiovascular disease before ever progressing to end-stage renal disease (ESRD).[2]

An important difference in rates of progression to ESRD among different racial and ethnic groups suggests that indices other than classic risk factors may determine how quickly an individual will lose renal function. Hsu et al demonstrated that although the incidence of chronic kidney disease is similar among African Americans and Caucasians, African Americans are five times more likely to progress to ESRD (Table 2).[12] When adjusted for age, gender, and diabetes, this increased risk for African Americans was only modestly affected. In addition, African Americans develop hypertension earlier and at a higher rate than other racial/ethnic groups and have increased risk of cardiovascular death, diabetes, and obesity.[13] However, these factors alone cannot explain the magnitude of the difference in the development of ESRD.

Relationship Between Renal Disease and Cardiovascular Disease

In the general population, chronic kidney disease is an established predictor of cardiovascular events. The US Renal Data System (USRDS) study showed that patients in a Medicare population who had been diagnosed with chronic kidney disease but who were not on dialysis had an absolute increase in the incidence of cardiovascular events of 9% compared to patients without chronic kidney disease (Figure 1). This difference translates into a 60% greater relative risk.[14]

The Heart Outcomes Prevention Evaluation (HOPE) study found similar results in patients who were aged 55 years or older and who were already at high risk of cardiovascular events. In this population, renal insufficiency was an independent predictor of cardiovascular events.[10] Twenty-two percent of patients with mild renal insufficiency (serum Cr ≥1.4 mg/dL [GFR <80 mL/min/1.73 m^2], but <2.3 mg/dL) experienced cardiovascular death, myocardial infarction (MI), or stroke over the 4-year follow-up period compared with 15% of patients without renal insufficiency (*P* <.001), an increased relative risk of 46%. The increased risk was proportional to serum Cr (Table 3).[10]

Table 2

Racial Differences in Progression of Chronic Renal Insufficiency (GFR 15-59 mL/min/1.73 m^2)[12]

	Prevalence per 100,000*	New ESRD Cases in 1996†/ 100 CRI Cases in 1991*
African Americans	2060	5
Whites	2520	1
P	.14	<.05

*Based on NHANES 1991 data.

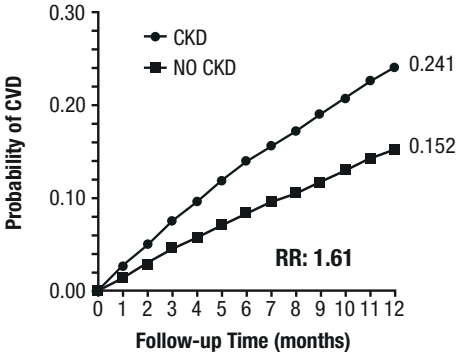
†Based on USRDS 1996 data.

GFR indicates glomerular filtration rate; ESRD, end-stage renal disease; CRI, chronic renal insufficiency.

In another study, Shlipak et al reported that renal insufficiency reduced survival among patients ≥65 years who were diagnosed with acute MI.[15] Patients with no renal dysfunction at baseline had a 1-year mortality rate of 24% compared with 46% in patients with mild renal insufficiency, and 66% in those with moderate renal insufficiency (*P*<.001). The risk of death was greatest during the first month following MI for individuals with mild-to-moderate renal dysfunction, but remained elevated during the first 6 months post-MI (Figure 2). Furthermore, the investigators found that post-MI treatment of patients with mild-to-moderate renal dysfunction was less aggressive than that of patients with no renal dysfunction.[15]

Figure 1

Probability of Incident Cardiovascular Disease (1998)[14]



Adapted from USRDS, 1998.

Cardiovascular Risk Factors and Renal Dysfunction

Although numerous observational studies have suggested a link between renal function and cardiovascular disease, whether renal insufficiency can promote cardiovascular disease remains open (Figure 3). Clearly, proteinuria is associated with cardiovascular risk, but studies of patients with renal dysfunction and minimal proteinuria offer compelling data to suggest that renal function per se modulates cardiovascular risk. By examining the relationship between renal function and traditional cardiovascular risk factors, the possibilities become apparent.

Hypertension

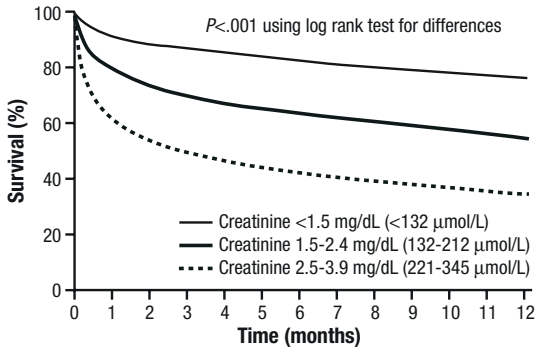
The interdependence of renal function and blood pressure is well established and can be explained in the simplest terms by the homeostatic forces regulating salt and water excretion. However, in patients with early stages of essential hypertension, excretion of salt and water is normal. The difference can be attributed to a shift in the pressure-natriuresis curve in the hypertensive setting such that excretion occurs at a higher blood pressure than in normal individuals.[16]

The association of hypertension with chronic kidney disease has been demonstrated in several clinical trials (Table 4, page 4). The NHANES III study found that 70% of the estimated 5.6 million individuals (3%) in the United States with renal insufficiency (men, serum Cr ≥1.6 mg/dL or women, serum Cr ≥1.4 mg/dL) have hypertension.[17] A positive correlation between serum Cr levels and hypertension also was found in the Heart Estrogen/progestin Replacement Study (HERS), in which 55% of women with normal renal function, 66% of women with mild renal dysfunction, and 77% of women with moderate renal dysfunction were hypertensive.[18]

In the Framingham study, significantly more women with mild renal insufficiency had hypertension (*P*<.0001) than individuals with normal renal function. The presence of mild renal disease did not significantly change the proportion of men with hypertension. However, mild renal insufficiency with cardiovascular comorbidity correlated strongly with adverse outcomes.[19] Furthermore, when patients with moderate or severe renal insufficiency were included in the analysis, the odds ratio for receiving antihypertensive treatment was significantly greater for both sexes.[20]

Figure 2

Unadjusted 1-Year Survival for 130,099 Elderly Patients After Myocardial Infarction According to Initial Serum Creatinine Levels



Reprinted with permission from Shlipak et al. *Ann Intern Med*. 2002;137:555-562.[15]

Table 3

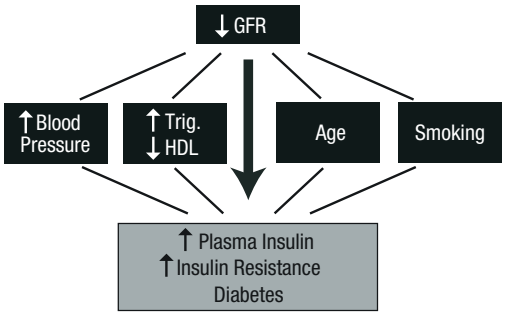
Renal Insufficiency and Cardiovascular Outcomes in the HOPE Trial[10]

Outcome	Serum Cr ≥1.4 mg/dL and <2.3 mg/dL (n=980) %	Serum Cr <1.4 mg/dL (n=8307) %	*P*
Acute MI	16.3	10.5	<.001
Stroke	5.0	4.0	.07
CV death	11.4	6.6	<.001
All death	17.8	10.6	.0065
Hospitalized CHF	6.0	2.9	.0115
Revascularization	19.6	16.9	.08

Cr indicates creatinine; MI, myocardial infarction; CV, cardiovascular; CHF, congestive heart failure.

Figure 3

Traditional Risk Factors for Cardiovascular Disease in Chronic Kidney Disease



The presence of chronic kidney disease in patients with hypertension has been shown to increase the risk of mortality in general, cardiovascular events, and cardiovascular mortality specifically.[21,22] Treatment for hypertension in the Hypertension Optimal Treatment (HOT) trial did decrease the number of cardiovascular events in this population but did not reduce serum Cr levels.[22]

Metabolic Syndrome and Diabetes

The association of diabetes, hypertension, and dyslipidemia was initially described more than 40 years ago. In the late 1980s, insulin resistance was recognized as a critical component of this metabolic profile, called syndrome X or metabolic syndrome. Since that time, a more complete understanding of metabolic syndrome has contributed to increased recognition of the neuroendocrine properties of tissues such as the adipose tissue and the endothelium. Previously, the adipose tissue and the endothelium were thought to serve relatively passive functions as a storage depot and selective barrier, respectively. The study of metabolic syndrome also has called attention to the fact that the increased cardiovascular risk associated with diabetes actually results from cardiovascular damage accrued in the years prior to the diagnosis of diabetes. More recently, the contribution of the kidney to glucose tolerance has also come under closer scrutiny.

Although impaired glucose tolerance has been known for many years to reflect a common comorbid condition in patients with renal failure, recent studies have demonstrated that insulin resistance and hyperinsulinemia occur early in the course of chronic kidney disease. In a population of patients with chronic renal disease, the mean insulin sensitivity index was significantly lower than for healthy controls. This observation held true even in patients with mild renal dysfunction (serum Cr <1.3 mg/dL). Regardless of the type of renal disease, insulin resistance was present in chronic kidney disease patients whose GFR was within the normal range, suggesting that impaired glucose tolerance occurs early in the development of chronic kidney disease (Figure 4).[23] In another study of compensatory hyperinsulinemia, Kubo et al showed that serum insulin, systolic and diastolic blood pressures, total serum cholesterol, and serum triglyceride levels each negatively correlated with the reciprocal of serum Cr concentrations (Table 5).[24] The findings from these studies suggest that renal dysfunction is a part of the metabolic syndrome and contributes to cardiovascular risk.

Obesity, also a component of metabolic syndrome, may account for approximately 65% of essential hypertension in women and 78% of essential hypertension in men, based on risk estimates from the Framingham Heart Study.[25] The precise mechanism by which obesity affects

Table 4

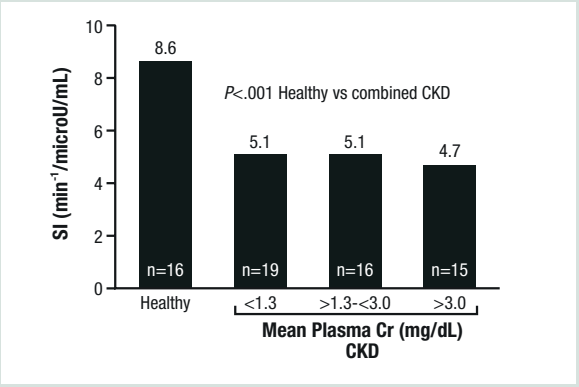
Observational Studies of Hypertension and Chronic Kidney Disease[17-22]

Study	Population	Definition of Renal Insufficiency	Outcome	Result
National Health and Nutrition Examination Survey (NHANES) III[17]	16,589 adults aged ≥17 years	Serum Cr Men: ≥1.6 mg/dL Women: ≥1.4 mg/dL	% with HTN	70%
Heart Estrogen/Progestin Replacement Study (HERS)[18]	2761 women	No renal insufficiency: Serum Cr <1.2 mg/dL Mild renal insufficiency: Serum Cr 1.2-1.4 mg/dL Moderate renal insufficiency: Serum Cr >1.4 mg/dL	% with HTN (*P* based on chi-square test for proportions and analysis of variance for continuous values)	None: 55% Mild: 66% Moderate: 77% (*P*<.001)
Framingham Heart Study[20]	6233 adults	Serum Cr (above sex-specific 95th percentile cutpoints from healthy reference sample) Men: ≥1.5 mg/dL Women: ≥1.4 mg/dL	OR for HTN treatment (95% CI)	Men: 1.75 (95% CI, 1.27-2.42) Women: 1.42 (95% CI, 1.07-1.87)
Framingham Heart Study (mild renal insufficiency)[19]	6233 adults	Serum Cr Men: 1.5-3.0 mg/dL Women: 1.4-3.0 mg/dL	% with HTN (*P* compared with control population without renal insufficiency)	Men: 34.3% (NS) Women: 39.3% (*P*=.0001)
Hypertension Detection and Follow-up Program (HDFP)[21]	10,940 adults	Serum Cr ≥1.7 mg/dL	Relative odds of death in 8 y (Z-score)	2.221 (Z score, 5.609)
Hypertension Optimal Treatment (HOT) Study[22]	18,790 patients with HTN	Serum Cr ≥1.5 mg/dL	Relative risk of major CV events (95% CI, *P* compared with serum Cr <1.5 mg/dL)	2.05 (95% CI, 1.47-2.88, *P*<.001)

Cr indicates creatinine; OR, odds ratio; HTN, hypertension; CV, cardiovascular; CI, confidence interval.

Figure 4

Relationship of Insulin Sensitivity Index and Plasma Creatinine (mg/dL)



Adapted with permission from Fliser et al. *Kidney Int*. 1998;53: 1343-1347.[23]

Table 5

Correlation of Serum Insulin, Blood Pressure, Total Cholesterol, and Triglycerides With Reciprocal of Serum Creatinine[24]

	Correlation Coefficients of 1/Serum Cr (*P*<.01 For All Listed Values)	
Parameter	**Men (n=1065)**	**Women (n=1381)**
Fasting insulin	−0.175	−0.082
Insulin	−0.163	−0.103
Systolic BP	−0.090	−0.090
Total cholesterol	−0.128	−0.093
Triglycerides	−0.115	−0.098

Cr indicates creatinine; BP, blood pressure.

blood pressure is not known. However, in animal models, and likely in humans, renal sympathetic nerves mediate sodium retention and hypertension in obesity.[26]

Leptin is a hormone excreted by the kidney, which is involved in the lipostat feedback loop to suppress food intake and increase energy expenditures. As such, leptin is a candidate for stimulating increased sympathetic activation in the kidney in obese individuals.[27] Strong correlations between insulin and leptin levels have been reported based on data from several different populations.[28,29] In addition, plasma leptin levels were significantly associated with elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, typical of metabolic syndrome.[30] Furthermore, in the West of Scotland Coronary Prevention Study plasma leptin levels were found to be a significant, independent risk factor of coronary heart disease.[31] Although leptin is excreted by the kidney, there are contradictory data linking leptin levels to renal function.

Dyslipidemias

Although elevated cholesterol levels are common among patients with stages 4 and 5 chronic kidney disease, there is little information about lipid abnormalities in mild-to-moderate renal insufficiency. An inverse correlation between serum lipoprotein(a) levels, but not other plasma lipids, and Cr_{CL} has been demonstrated in hypertensive patients with mild-to-moderate renal insufficiency. The frequency of distribution of apolipoprotein(a) isoforms was similar in normal patients and those with early renal failure, suggesting that decreased renal catabolism is a probable mechanism of lipoprotein(a) elevation in these patients.[32] In the HERS study, triglyceride and lipoprotein(a) levels increased with increasing serum Cr levels (Table 6).[18] Although these findings are inconclusive, the relationship between early renal dysfunction and dyslipidemia, particularly more subtle changes in remnants and oxidized lipoproteins, may prove to be a fruitful avenue of investigation.

Nontraditional Risk Factors

Observational studies have demonstrated a connection between renal function, cardiovascular disease, and metabolic syndrome with nontraditional cardiovascular risk factors (Figure 5, page 6). The criteria for defining nontraditional risk factors are listed in Table 7, page 6.[33] A number of nontraditional cardiovascular risk factors have been identified that meet the first two or three criteria; however, with the exception of anemia, limited data are available from clinical trials. All of the risk factors listed in Table 7 have been shown to be associated with metabolic syndrome.

Table 6

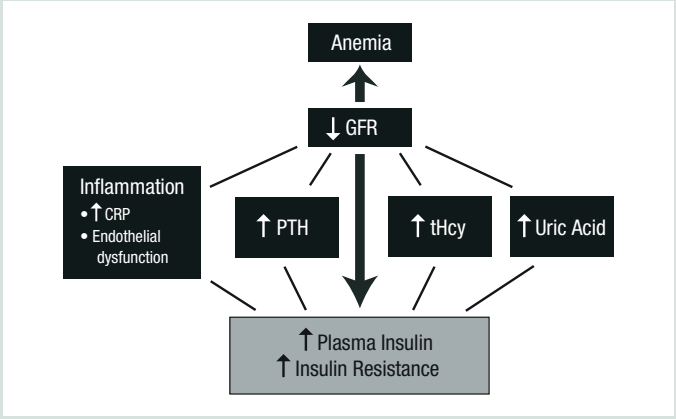
Decreased Glomerular Filtration Rate Correlates With Increased Plasma Lipids[18]

	Serum Cr (mg/dL)			
Plasma lipid (mg/dL)	**<1.2 (n=2012)**	**1.2-1.4 (n=567)**	**>1.4 (n=182)**	***P***
LDL	145 ± 38	145 ± 36	147 ± 43	.72
HDL	51 ± 13	49 ± 13	49 ± 14	.12
Triglycerides	160 ± 61	168 ± 64	182 ± 67	.002
Lp(a)	33 ± 32	35 ± 33	38 ± 36	.05

Cr indicates creatinine; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein(a).

Figure 5

Nontraditional Risk Factors for Cardiovascular Disease



tHcy indicates total homocysteine.

Inflammation

Chronic inflammation is now widely accepted as an important factor in the pathogenesis of atherosclerotic vascular disease. Therefore, it is not surprising that C-reactive protein (CRP), a marker of inflammation, is a strong predictor of MI, stroke, and peripheral arterial disease independent of traditional cardiovascular risk factors.[34-37] Panichi et al found that in 25% of patients with renal insufficiency who were not on dialysis (mean Cr_{CL}, 52 ± 37 mL/min), CRP levels were above normal (5 mg/L). In the subpopulation of patients with Cr_{CL} rates <20 mL/min, the proportion of patients with CRP levels above 5 mg/L rose to 56%. A related inflammatory mediator, interleukin-6, also was significantly elevated in patients with Cr_{CL} rates of <20 mL/min, compared with those with Cr_{CL} rates >20 mL/min (P <.05).[38]

Stuveling et al conducted the first large-scale study of the association between CRP levels and loss of renal function (Table 8). In a study of 7317 nondiabetic patients, the odds ratio (OR) for reduced Cr_{CL} was significantly higher in individuals with CRP levels in the third and fourth quartiles (OR 1.6, P<.01; OR 1.8, P<.005, respectively).[39] Conversely, Stam et al found that CRP levels were significantly increased in individuals with Cr_{CL} rates in the lowest quartile (mean Cr_{CL} rate, 16.3 ± 5.4 mL/min). Cr_{CL} also was an independent determinant of the inflammatory activity score, calculated as the sum of CRP + secretory phospholipase A_2 + soluble intracellular adhesion molecule-1 (sICAM-1)/3 (β=−0.31, P=.025).[40]

Endothelial Dysfunction

Endothelial dysfunction is characterized by increased plasma levels of endothelial-derived atherogenic proteins and by reduced endothelium-dependent vasodilation. In the previously cited study by Stam et al, Cr_{CL} was significantly related to the endothelial function score, calculated as the sum of the atherogenic markers (von Willebrand factor + soluble vascular cell adhesion molecule-1 [sVCAM-1] + sICAM-1 + E-selectin + plasminogen activator inhibitor-1-selectin + tissue-type plasminogen activator)/6 (r=−0.43, P<.001).[40] When individual markers of endothelial function were analyzed separately, Cr_{CL} was a significant determinant of von Willebrand factor, sICAM-1, and sVCAM-1 (Table 9).[40]

Hyperhomocysteinemia

Elevated plasma levels of homocysteine are toxic to vascular endothelium, inducing endothelial dysfunction and acting as a risk factor for atherosclerosis that is independent of traditional cardiovascular risk factors.[41-47] In addition, elevated plasma homocysteine concentrations are present from an early stage of renal dysfunction and increase with progressive renal failure.[48-50] Jungers et al demonstrated that hyperhomocysteinemia is an independent risk factor for atherosclerotic cardiovascular accidents in predialysis chronic kidney disease patients.[51]

Table 7

Criteria for Nontraditional Cardiovascular Risk Factor Status in Chronic Kidney Disease and Association With Metabolic Syndrome[33]

	Increased CRP	Endothelial Dysfunction	Homocysteinemia	Increased PTH	Increased Uric Acid	Anemia
Plausible mechanism	Yes	Yes	Yes	Yes	Yes	Yes
Risk factor increases with severity of CKD	Yes	Yes	Yes	Yes	Yes	Yes
Risk predicts CVD in CKD	Yes	?	Yes			
Treatment improves outcomes	No data	No data	No data	No data	No data	No data
Risk for metabolic syndrome	Yes	Yes	Yes	Yes	?	?

CRP indicates C-reactive protein; PTH, parathyroid hormone; CKD, chronic kidney disease; CVD, cardiovascular disease.

In a comparison of factors that affect fasting plasma homocysteine in the Framingham Offspring cohort, Jacques et al found that serum Cr was a significant determinant of fasting homocysteine levels.[52] Further analysis of this population established a relationship between hyperhomocysteinemia, Cr_{CL}, and hyperinsulinemia. The authors suggest that elevated homocysteine levels coupled with renal insufficiency may contribute to the increased cardiovascular risk associated with metabolic syndrome.[53]

Parathyroid Hormone

Secondary hyperparathyroidism frequently accompanies early chronic kidney disease. Two groups of investigators have reported that serum parathyroid hormone (PTH) levels are increased with increasing renal dysfunction. These groups reported that hyperparathyroidism secondary to chronic kidney disease occurs early in the disease process and probably is related to abnormal regulation of the biosynthesis of 1,25-dihydroxyvitamin D_3 (Table 10).[54,55]

Of note is the finding by Wareham et al that insulin resistance also correlates with elevated PTH levels and serum calcium. The correlation was independent of age, obesity, season, and 25-hydroxyvitamin D levels. This association of glucose tolerance and PTH levels suggests another mechanism whereby renal dysfunction may contribute to metabolic syndrome.[56]

Some evidence indicates that PTH may be a vascular toxin, although this hypothesis remains controversial. In patients with primary hyperparathyroidism, hypertension increased the annual mortality rate. During the 10-year follow-up period, cardiovascular disease was directly related to serum calcium level, adenoma weight, osteitis fibrosa, and serum Cr level. Cardiovascular disease was inversely related to GFR. These findings suggest that cardiovascular disease is part of hyperparathyroidism rather than a frequent comorbidity (Table 11, page 8).[57]

Uric Acid Toxicity

Despite the positive correlation between elevated uric acid levels and cardiovascular disease in the general population, an independent causal role has not been established. In the Framingham Study, for example, hyperuricemia was not shown to be an independent risk factor for cardiovascular disease. However, in the NHANES I study, serum uric acid levels were significantly associated with the incidence of cardiovascular events, and the association was stronger in African Americans than in Caucasians. This difference was true for both men and women.[58,59] Evidence of elevated serum uric acid as a risk factor is more convincing for patients with hypertension and congestive heart failure (CHF) and likely reflects diminished renal function in patients with these disorders.[60,61]

Table 8

Odds Ratios of Diminished Filtration According to C-Reactive Protein Levels

	Quartile of CRP (mg/L)			
	Q1	Q2	Q3	Q4
Parameter	**<0.54**	**0.54-1.20**	**1.22-2.76**	**>2.76**
Odds of decreased Cr clearance*	1.0	1.3	1.7	1.9
95% CI	–	0.8-2.0	1.1-2.5	1.3-2.9
P	–	NS	<.05	<.005

*After adjustment for age, gender, body mass index, glucose, blood pressure, antihypertensive use, cholesterol, lipid-lowering therapy, albuminuria, and smoking.

CRP indicates C-reactive protein; Cr, creatinine; CI, confidence interval; NS, not significant.

Adapted with permission from Stuveling et al. *Kidney Int*. 2003;63:654-661.[39]

Table 9

Glomerular Filtration Correlates With Markers of Endothelial Dysfunction[40]

	Quartile of Cr Clearance (mL/min/1.73 m²)			
Parameter	**Q1 100 ± 22 (n=20)**	**Q2 67 ± 9 (n=20)**	**Q3 40 ± 8 (n=20)**	**Q4 16 ± 5 (n=20)**
CRP (mg/L)	1.7 ± 2.5	2.3 ± 1.5	4.5 ± 11.1	5.0 ± 4.1*†
von Willebrand factor (%)	91	111*	159*†	173*†
sVCAM-1 (ng/mL)	1126 ± 338	1080 ± 249	1556 ± 444*†	1796 ± 594*†

**P*<.05 compared to Q1.

†*P*<.05 compared to Q2.

Cr indicates creatinine; CRP, C-reactive protein; Q, quartile; sVCAM-1, soluble vascular adhesion molecule-1.

Table 10

Calcium-Regulating Hormones in Patients With Chronic Renal Failure

	Intact PTH (pmol/L) (Normal range, 1.2-6.0)		1,25 $(OH)_2D_3$ (pg/mL) (Normal range, 35-90)	
GFR (mL/min/1.73 m²)	**Median (range)**	**No. Above Normal**	**Median (range)**	**No. Below Normal**
>90	3.5 (2.3-4.9)	0/22	48 (23-112)	4/22*
60-90	5.6 (2.2-13.0)	6/19	32 (20-66)	9/19
40-60	8.1 (2.9-24.0)	12/22	34 (22-74)	11/22
20-40	13.0 (5.4-59.0)	20/22	26 (17-39)	18/20†

*Also 3/22 values were above normal in this assay.

†Values were available from 20/22 patients.

PTH indicates parathyroid hormone; GFR, glomerular filtration rate.

Reprinted with permission from Reichel et al. *Nephrol Dial Transplant*. 1991;6: 162-169.[55]

Table 11

Correlation Between Primary Hyperparathyroidism and Cardiovascular Disease Over 10 Years Following Parathyroidectomy[57]

	P (Positive Correlation)	
Parameter	CVD (25% of Population)	HTN (55% of Population)
Adenoma weight	.014	.029
Osteitis fibrosa (9%)	.03	NS
Osteoporosis (21%)	<.001	<.001
Serum Cr	<.001	<.001

CVD indicates cardiovascular disease; HTN, hypertension; NS, not significant; Cr, creatinine.

Anemia

Decreases in hemoglobin levels and systolic blood pressure have been shown to be predictors of left ventricular hypertrophy (LVH) in patients with mild-to-moderate chronic kidney disease (Table 12). A high prevalence of LVH is found, in turn, in early chronic kidney disease.[62]

Changes from baseline hemoglobin levels are as important as the presence of absolute anemia. These findings suggest that early control of anemia may improve outcomes for patients at high risk of LVH. Silverberg et al reported that correction of anemia in patients with CHF and chronic kidney disease resulted in a significant improvement in heart failure, ejection fraction, and frequency of hospitalization (Table 13).[63] Ironically, certain antihypertensive medications, including angiotensin-converting enzyme (ACE) inhibitors and calcineurin inhibitors, may induce or exacerbate anemia.[62]

Taken in sum, evidence strongly supports the hypothesis that mild-to-moderate renal dysfunction is an independent risk factor for cardiovascular disease and that treatment of modifiable risk factors can reduce cardiovascular risk. Although most of the studies reported here are small and observational, findings implicate neuroendocrine effects of the kidney in metabolic syndrome and in the development of cardiovascular disease. Whether early intervention can favorably affect the posttransplant population remains an interesting possibility.

Table 12

Odds Ratio for Left Ventricular Hypertrophy in Chronic Kidney Disease (Calculated Creatinine Clearance, 25-75 mL/min)[62]

Risk Factor	Change From Baseline	OR (95% CI)	*P*
Decreased hemoglobin	−0.5 g/dL	1.32	.004
Systolic BP	+ 5 mm Hg	1.11	.01

OR indicates odds ratio; CI, confidence interval; BP, blood pressure.

Cardiovascular Disease After Renal Transplantation

Transplantation offers a survival advantage over maintenance dialysis for patients with ESRD.[64] The survival advantage is primarily due to a decrease in mortality from cardiovascular disease and infectious disease. Furthermore, this survival advantage is maintained despite immunosuppressive therapy, which can exacerbate hypertension, cause or worsen existing diabetes mellitus, and contribute to anemia.

Despite the improved survival posttransplant, cardiovascular mortality accounts for 37% of the deaths among renal transplant recipients, well above that of the general population (Figure 6).[14,65,66]

Analysis of 58,900 adult patients registered in the USRDS who had received a renal transplant showed that serum Cr values of >1.5 mg/dL were associated with a significant and progressive increase in the risk of cardiovascular death (Figure 7).[67]

However, whether the increased risk of cardiovascular disease in renal transplant recipients can be attributed to the same factors as in the general population is not entirely understood. Kasiske et al found that cardiovascular risk calculated from the Framingham Heart Study did predict risk of ischemic heart disease in patients after more than 1 year posttransplant, but the risk tended to be underestimated. The risk of

Table 13

Correction of Anemia in Patients With Congestive Heart Failure and Chronic Kidney Disease[63]

Study Parameter	Baseline	After Treatment*
Hemoglobin (g/dL)	10.3	13.1
Hematocrit (%)	30.6	41.8
NYHA class (0-4)	3.8	2.7
Hospitalizations per patient (n)	3.7	0.2
Ejection fraction	33.2	39.6

*$P \leq .05$ for all values.

NYHA indicates New York Heart Association.

Adapted with permission from Silverberg et al. *Perit Dial Int*. 2001;21(suppl 3):S236-S240.

cardiovascular events associated with diabetes mellitus was markedly underestimated. The risk of ischemic heart disease in men with diabetes in the general population was increased by 53% compared to nondiabetic patients. The risk for diabetic men who were also renal transplant recipients was almost threefold higher than nondiabetic men in the general population.[68]

Pretransplantation Risk Factors

The incidence of posttransplant cardiovascular events is affected by some pretransplant risk factors. Age, male gender, cigarette smoking, diabetes, ischemic heart disease, cerebrovascular disease or peripheral vascular disease prior to transplantation are predictors of higher posttransplant cardiovascular risk.[69]

Hypertension

Hypertension may contribute to nonimmunologic, long-term allograft transplant failure. At 1 year posttransplant, 75% of transplant recipients are hypertensive (SBP ≥130 mm Hg) (Figure 8).[70] Moreover, 5-year graft survival decreased in association with higher levels of systolic blood pressure.[70] Whether treatment of hypertension can enhance allograft survival remains less certain. Treatment of transplant recipients with the angiotensin-receptor blocker losartan significantly reduced arterial hypertension (*P*=.00000013), serum Cr levels, and the rate of increasing serum Cr levels (*P*=.014). Proteinuria also was decreased to a statistically significant degree (*P*=.0001). These findings suggest that antihypertensive therapy may provide posttransplant renoprotection, although the clinical effects of losartan may not be limited to reducing blood pressure.[71]

However, ACE inhibitors and angiotensin-receptor blockers reduce erythropoietin levels and are used to treat posttransplant erythrocytosis. Resulting reduction of hemoglobin levels can be detrimental if anemia is induced or worsened. For that reason, the potential for these agents to provide renoprotection and reduce cardiovascular risk must be weighed against any increased cardiovascular risk related to anemia.[72]

Inflammation

Because inflammation is related to allograft rejection, pretransplantation CRP levels were evaluated as predictors of allograft rejection, cardiovascular events, and renal dysfunction over 5 years by Lauzurica et al. In this study of 79 patients undergoing cadaveric kidney transplantation, pretransplant CRP levels were statistically correlated with serum Cr levels at 5 years posttransplant. Although the difference was not statistically significant, pretransplant CRP levels were higher in individuals who later experienced cardiovascular events than in those who did not. The lack of significant association between pretransplant CRP levels and cardiovascular events may be attributed to small sample size and short duration of follow-up.[73]

Figure 6

Mortality in Renal Transplant Recipients[14,65,66]

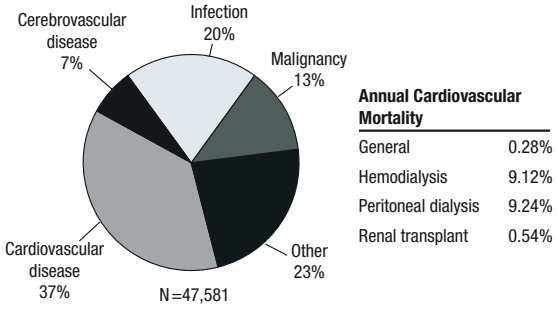
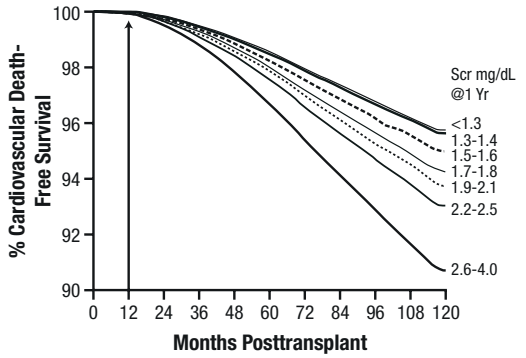


Figure 7

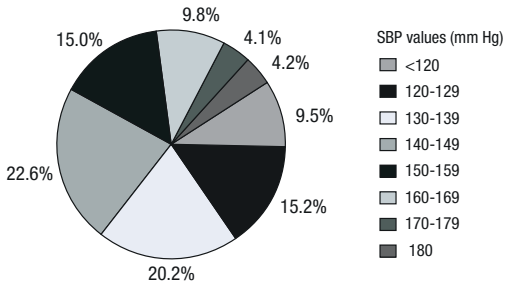
Cardiovascular Death-Free Survival by Serum Creatinine Levels at 1 Year Posttransplant



Reprinted with permission from Meier-Kreische et al. *Transplantation*. 2003;75:1291-1295.[67]

Figure 8

Incidence of Hypertension at 1 Year Posttransplant (N=29,751)[70]



SBP indicates systolic blood pressure
Total exceeds 100% due to rounding.

Hyperhomocysteinemia

Plasma total homocysteine levels have been shown to be inversely related to renal function. Although the etiology of hyperhomocysteinemia in renal disease is not completely understood, reduced plasma homocysteine clearance, rather than increased production, has been implicated.[74] Therefore, it is not surprising that renal transplant recipients have a greatly increased prevalence of hyperhomocysteinemia compared with the general population. However, the prevalence, etiology, and treatment of hyperhomocysteinemia in renal transplant recipients are very similar to the much larger population of patients with chronic renal insufficiency. Clinical trials are ongoing to determine whether reducing serum homocysteine levels in renal allograft recipients posttransplant will improve cardiovascular outcomes.[75]

Hyperparathyroidism

In one recent study, Suwelack et al reported that intact PTH levels significantly decreased following renal transplantation ($P<.01$) in 55 normotensive patients.[76] Although this study did not evaluate cardiovascular outcomes, normalization of PTH levels was positively and independently correlated with a significant decrease in common carotid artery intima and media thickness ($P<.01$). Atherosclerotic lesions in patients with ESRD typically have higher intima and media thickness than lesions in the general population.[77] The investigators concluded that increased intima and media thickness may contribute to the high cardiovascular morbidity and mortality in renal transplant recipients.[76]

Special Cardiovascular Risk Factors in Transplant Recipients

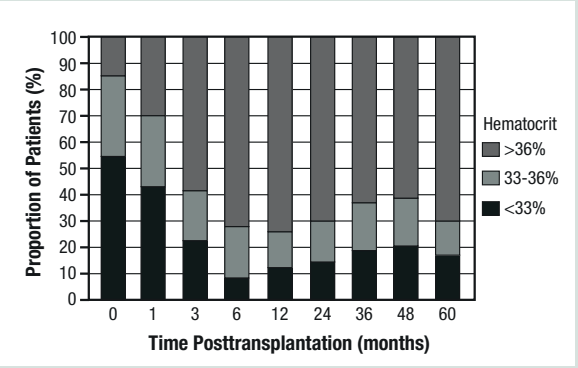
Posttransplant cardiovascular risk is complicated by the effects of immunosuppressive therapy on renal function and anemia. The incidence of hemolytic uremic syndrome (HUS) with or without rejection has been reported to be approximately 10% in renal transplant recipients receiving cyclosporine[78] or tacrolimus. These effects of calcineurin-inhibitor therapy may contribute to the higher incidence of anemia and renal dysfunction seen in transplant recipients.

Although transplantation improves anemia initially, over time hematocrit levels begin to decrease. This decrease is associated most strongly with the level of renal function. In a retrospective cohort study, Mix et al found that hematocrit levels increased during the first 6 months following transplantation and began to decrease between 6 months and 12 months posttransplant (Figure 9). Furthermore, treatment for anemia was suboptimal. Even among those patients with hematocrit values <30%, fewer than half were receiving iron supplementation or recombinant erythropoietin.[79]

The observed decrease in hematocrit correlated with decreasing GFR (Figure 10). Among patients with a GFR ≥90 mL/min/1.73 m^2, 11% and 7% had some degree of anemia at 6 months and 12 months posttransplant, respectively. In contrast, in patients with a GFR <30 mL/min/1.73 m^2, some degree of anemia was evident in 60% and 76% at 6 and 12 months, respectively.[79]

Figure 9

Changes in Hematocrit After Kidney Transplantation

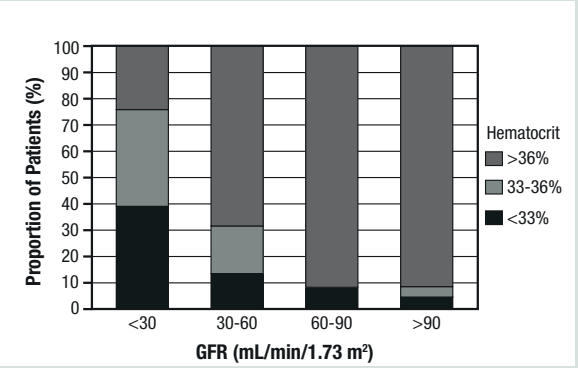


Reprinted with permission from Mix et al. *Am J Transplant*. 2003; 3:1426-1433.[79]

In renal transplant recipients with type 1 diabetes, hematocrit levels within the first 30 days posttransplant have been shown to be predictive of early cardiovascular events. The relative risk of a cardiovascular event in the first 26 weeks posttransplant was significantly reduced in patients with hematocrit values >30% compared with those whose hematocrit values were <30% (RR, 0.237; $P=.015$). Furthermore, 10.4% of patients with average hematocrit values ≤30% during the first 6 months posttransplant experienced at least one cardiovascular event, which was significantly greater than the cardiovascular event rate in patients with average hematocrit values >30% during the same follow-up period ($P<.002$) (Figure 11).[80]

Figure 10

Hematocrit Levels According to Kidney Function



Reprinted with permission from Mix et al. *Am J Transplant*. 2003; 3:1426-1433.[79]

Immunosuppressive therapy has clearly extended allograft survival and reduced morbidity among transplant recipients. However, the long-term use of calcineurin inhibitors can increase renal insufficiency. These agents and corticosteroids can increase the incidence of hypertension, hyperglycemia, and hyperlipidemia, thus contributing to elevated cardiovascular risk. Although the proliferation signal inhibitors or TOR inhibitors (sirolimus and everolimus) are inherently nonnephrotoxic, they are associated with more significant hyperlipidemia than other immunosuppressive agents. It remains an open question whether these agents will also be associated with more or less cardiovascular risk (Table 14).

Management of cardiovascular risk in posttransplant patients must take into account the interplay of immunosuppressive therapy and cardiovascular risk. Screening and treatment of anemia, combined with optimal immunosuppressive therapy, presumably can improve cardiovascular outcomes in this vulnerable patient population.

SUMMARY AND CONCLUSIONS

In the general population, individuals with chronic kidney disease are at a high risk for cardiovascular events. Other well-known traditional cardiovascular risk factors, such as hypertension, metabolic syndrome, and dyslipidemia, also are associated with increased risk of chronic kidney disease. In addition, a number of nontraditional cardiovascular risk factors that are markers of inflammation and endothelial dysfunction also are predictive of chronic kidney disease. Evidence suggests that the relationship between chronic kidney disease and cardiovascular disease may be bi-directional.

Cardiovascular risk in posttransplant patients shares many similarities with cardiovascular risk in the general population, as well as in those with mild-to-moderate renal dysfunction. Although renal transplantation reduces the risk of cardiovascular events compared to maintenance dialysis, the transplant population remains at high risk of cardiovascular morbidity and mortality. In addition to the cardiovascular risk factors shared with the general population, status of pretransplant cardiovascular risk factors, posttransplant renal function, and immunosuppressive therapy are predictive of cardiovascular risk in renal transplant recipients.

Findings suggest that further studies are needed to understand the etiology of cardiovascular disease in posttransplant patients. In addition, early and aggressive treatment of hypertension, glucose intolerance, dyslipidemia, anemia, and other conditions common in individuals with early renal disease may improve long-term outcomes posttransplant and warrants further investigation. Immunosuppressive regimens that are not calcineurin antagonist- or corticosteroid-based may be preferable to reduce cardiovascular risk.

The next CLINICIAN in this series of educational activities will focus in greater detail on the relationship between cardiovascular risk and renal function in the renal transplant population.

Figure 11

Rate of Cardiovascular Events (Cardiovascular Death, MI, or Hospitalization for CHF or Angina) in Recent Type 1 Diabetic Renal Transplant Recipients Based on Anemia in the First 6 Months Posttransplant

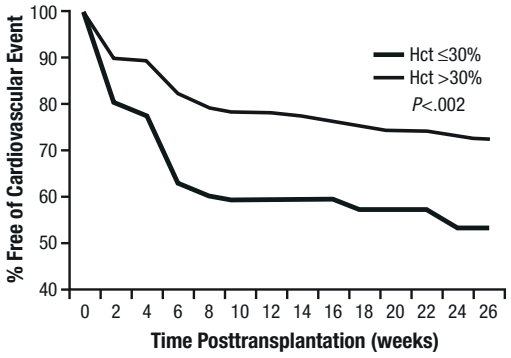


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Table 14

Side Effect Profiles of Immunosuppressive Agents

Side Effect	Cyclosporine	Tacrolimus	Sirolimus	Steroids	MMF
Hypertension	++	+	ϕ	++	ϕ
Hyperglycemia	+	++	ϕ	+++	ϕ
Renal insufficiency	++	++	ϕ	ϕ	ϕ
Hyperlipidemia	++	+	++	++	ϕ
Hyperkalemia	+++	+++	ϕ	ϕ	ϕ
Tremor	ϕ	+	ϕ	ϕ	ϕ
Hirsutism	+	ϕ	ϕ	ϕ	ϕ
Gingival hyperplasia	+	ϕ	ϕ	ϕ	ϕ
Hypophosphatemia	++	++	+	ϕ	ϕ
Osteoporosis	±	±	ϕ	+++	ϕ
Malignancy	+	+	?	ϕ	+

MMF indicates mycophenolate mofetil.
Adapted from Martin Zand, MD.

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Epidemiology of Renal Dysfunction and Cardiovascular Disease

CME Post-test and Evaluation

Release Date: March 2004 Expiration Date: March 31, 2005

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Post-test Answer Key

1. A B C D E	3. A B C D E	5. A B C D E	7. A B C D E	9. A B C D E
2. A B C D E	4. A B C D E	6. A B C D E	8. A B C D E	10. A B C D E

POST-TEST

1. The primary objective of the Chronic Renal Insufficiency Cohort (CRIC) study is to:
   a. Monitor the increased incidence and prevalence of chronic renal insufficiency
   b. Assess the efficacy of treating glucose intolerance in chronic renal insufficiency
   c. Conduct an observational study of the risk of glucose intolerance in chronic renal insufficiency
   d. Identify and treat patients with chronic renal insufficiency who are at highest risk of cardiovascular events
   e. None of the above

2. African Americans are:
   a. Five times more likely to progress to end-stage renal disease than Caucasians
   b. Five times more likely to have chronic renal disease than Caucasians
   c. Five times less likely to progress to end-stage renal disease than Caucasians
   d. Five times less likely to have chronic renal disease than Caucasians
   e. None of the above

3. Mild chronic kidney disease (serum Cr ≥1.4 mg/dL but <2.3 mg/dL):
   a. Is not associated with increased cardiovascular risk in patients over the age of 55 years
   b. Is associated with a 46% increased relative risk of cardiovascular death, myocardial infarction, and stroke
   c. Is associated with increased cardiovascular risk, which is proportional to serum creatinine levels
   d. b and c
   e. None of the above

4. In the Framingham Heart Study, compared to individuals with normal renal function:
   a. Significantly more women with mild chronic kidney disease were hypertensive
   b. The association between mild chronic kidney disease and hypertension was not statistically significant in women
   c. Significantly more men with mild chronic kidney disease were hypertensive
   d. The association between mild chronic kidney disease and hypertension was not statistically significant in men
   e. None of the above

5. Metabolic syndrome is a constellation of symptoms that:
   a. Is associated with progression to type 2 diabetes
   b. Includes dyslipidemia, hypertension, hyperinsulinemia, obesity, and insulin resistance
   c. Is associated with increased cardiovascular risk
   d. Are negatively correlated with the reciprocal of serum creatinine concentrations
   e. All of the above

6. Typically, in mild-to-moderate renal insufficiency:
   a. Lipoprotein(a) levels are increased
   b. LDL cholesterol levels are elevated
   c. HDL cholesterol levels are elevated
   d. Triglyceride levels are decreased
   e. Lipoprotein(a) levels are decreased

7. In predialysis patients with chronic kidney disease, C-reactive protein levels are:
   a. Statistically similar to those with normal renal function
   b. Higher in patients with creatinine clearance of <20 mL/min than those with creatinine clearance of >20 mL/min
   c. Associated with decreased serum levels of interleukin-6
   d. Lower in patients with creatinine clearance of <20 mL/min than those with creatinine clearance of >20 mL/min
   e. Lower in patients with creatinine clearance of <20 mL/min than those with normal renal function

8. Renal transplant recipients have:
   a. Improved survival compared to patients on dialysis
   b. An approximate 37% cardiovascular mortality rate
   c. Significant and progressive risk of cardiovascular death if their serum creatinine levels are >1.5 mg/dL
   d. All of the above
   e. None of the above

9. Anemia in renal transplant recipients:
   a. Is associated with renal dysfunction
   b. Can be complicated by use of calcineurin inhibitors
   c. Within 30 days of transplantation is predictive of early cardiovascular events
   d. May improve during the first 6 months following transplantation
   e. All of the above

10. In renal transplant recipients, the highest risk of hypertension and renal insufficiency is associated with treatment with:
    a. Corticosteroids
    b. Cyclosporine
    c. Tacrolimus
    d. b and c
    e. All of the above

Epidemiology of Renal Dysfunction and Cardiovascular Disease

Program Evaluation

The University of Minnesota would appreciate your comments regarding the quality of the information presented.

1. The program objectives were fully met.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree

3. The educational activity has enhanced my professional effectiveness and improved my ability to treat/manage patients.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

4. The educational activity has enhanced my professional effectiveness and improved my ability to communicate with patients.

   ❑ Strongly Agree ❑ Agree ❑ Disagree ❑ Strongly Disagree ❑ N/A

5. The information presented was *without* promotional or commercial bias.

   ❑ Agree ❑ Disagree

6. What changes will you make in your practice as a result of participating in this program?

   _____

   _____

7. Comments/suggestions regarding *this* material.

   _____

   _____

8. Recommendations for *future* presentations.

   _____

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